Remarks

The present claims are claims 7-16. Favorable reconsideration of this application is respectfully requested.

Initially, it is noted that a Preliminary Amendment was filed on September 18, 2003 (i.e., concurrently with the filing of this continuing application), in which original claims 1-6 were canceled and claims 7-16 were presented. This Preliminary Amendment also included detailed remarks addressing various cited references of record. In any event, entry of this previous Preliminary Amendment is requested, and the remarks *infra* will be directed towards the claims on file (i.e., claims 7-16).

Additionally, although Applicant believes the next Action should be a Notice of Allowance, if a rejection is maintained, Applicant understands a Final Rejection would be premature since no rejection of claims 7-16 has yet been made by the Office.

Claims 1-4 were rejected under 35 USC 102(b) as anticipated by Mazuel et al. (US 4,861,760). The rejection states that Mazuel et al. teach the use of dexamethasone sodium phosphate in combination with mannitol, EDTA and benzalkonium chloride in a gel form for ophthalmic use.

As noted above, the pending claims are actually claims 7-16. Independent claim 7 is directed to an ophthalmic preparation that is a gel, which comprises dexamethasone dihydrogenphosphate disodium as the active agent, and which has a pH value above 7.3.

Such claimed ophthalmic preparations are clearly novel in view of Mazuel et al. Mazuel et al. discloses in Example 3 dexamethasone phosphate solutions (that may or may not turn into gels, and if so, only upon contact with the eye's liquids). At column 2, lines 16 et seq., Mazuel et al. explicitly states that the invention relates to a pharmaceutical composition that "is intended to be administered as a non-gelled liquid form and is intended to gel in situ" meaning that the Mazuel et al. preparation forms a gel only upon contact with the physiological fluid, namely, human lacrimal fluid. Such statements are repeated throughout the cited reference; see, for example, column 2, lines 30-34:

> "the composition, which takes the form of a liquid before its introduction into the eye, undergoes a liquid-gel phase transition, and hence changes from the liquid phase to the gel phase, once it is introduced into the eye, as a result of the ionic strength of the physiological fluid which is in this case, the lacrimal fluid.

In fact, Mazuel et al. teaches away from gel preparations; see, for example, column 2, lines 56 to 61:

> "Furthermore, in the case of already gelled or semi-gelled solid compositions, it is not possible to administer them by volumetric means, especially when they come from a multi-does container."

The rejection further references the Examples at columns 7-8 of Mazuel et al. However, these examples are liquid solutions that turn into gels upon contact with the lacrimal fluid. This behavior of the ophthalmic liquid solutions of Mazuel et al. is due to the specific polysaccharide Gelrit®. See, also, column 4, lines 59 et seq., where Mazuel et al. discloses adding acetic acid, if necessary, to avoid gelling of Gelrite solutions; in other words, Mazuel et al. again teaches against gel forms of the solutions, prior to administration to the eye.

Applicant is mindful that the Examiner is entitled to give the claims their broadest reasonable interpretation. However, it is submitted that the present claims do not read on a formulation that gels upon exposure to eye fluid. First, claim 7 clearly states the preparation has the form of a gel. Second, claim 7 stats the preparation has a pH above 7.3 – what would the pH value of the Mazuel et al. formulation be after contacting eye fluid? There is no evidence in Mazuel et al. that such later-formed gels have a pH value above 7.3; in fact, the properties of the later-formed gels are not disclosed at all in this reference.

As Mazuel et al. is only concerned with the aforementioned ophthalmic non-gel solutions, the gel formulations of the present application are clearly not suggested by this reference. In contract, Mazuel et al. teaches away from the gel formulations of the present invention, in that Mazuel et al. expressly requires a solution instead of a gel.

Claims 5 and 6 were rejected under 35 USC 103(a) as unpatentable over Mazuel et al. (US 4,861,760) and Rozier (US 5,304,559).

Rozier discloses pharmaceutical compositions containing at least one 4-quinolone derivative. Rozier does not cure the deficiencies of Mazuel et al., discussed above.

First, as pointed out above, Mazuel et al. teaches away from gel preparations as claimed. Rozier does not cure this deficiency.

Second, Rozier is concerned with specific ophthalmic preparations containing 4-quinolinone derivatives. Rozier is concerned with preventing crystal growth of these compounds in suspension. There is no mention of storage stable dexamethasone-containing formulations, nor is there any indication that a pH value above 7.3 may be used to increase the stability of a pharmaceutical preparation. In contrast, Rozier teaches that in order to obtain increased stability, an active compound has to be complexed with a certain divalent metal ion.

Third, the rejection alleges that these references also make clear that the use of the claimed pH in ophthalmic field is old. Applicant respectfully submits that such a broad statement does not adequately consider the evidence of record. For example, if dexamethasone dihydrogen phosphate disodium is used as the active compound, one encounters the problem that at pH values around 7.0, stability is reduced so that gel formulations of this compound are not suitable for long term storage conditions as required for pharmaceutical preparations. Why would one skilled in the art select a pH value above 7.3 from the cited references?

Additionally, in the previous Preliminary Amendment, Applicant submitted stability data for an ophthalmic gel preparation of dexamethasone dihydrogenphosphate disodium. Formulation A corresponded to the presently claimed invention. Formulation B is a similar formulation but the pH value was adjusted to 6.3 to 7.3. As evident from the first row, there is an unacceptable decrease in the amount of dexamethasone dihydrogenphosphate disodium of at least 14% for Formulation B. In contrast, Formulation A of the present invention exhibited only 1% decomposition of dexamethasone dihydrogenphosphate after 18 months.

The relevant data from the attached sheets is reproduced below, noting that supplemental supporting information was provided in the Preliminary Amendment.

Formulation A

Component	Amount (g)	Weight %
Carbopol 980	3.00	0.300
Dexamethasone-Na-Phosphate	1.107	0.1107
Cetrimide	0.100	0.0100
Na-edetate	0.100	0.0100
Sorbitol	49.00	4.900
NaOH	1.50	0.15
Water	945.193	94.5193
Total	1000.00	100%
pH Specification	7.6-8.0	

Formulation B

Component	Amount (g)	Weight %
Carbopol 980	1.5	0.30
Dexamethasone-Na-Phosphate	0.4925	0.09850
Cetrimide	0.05	0.01
Na-edetate	0.05	0.01
Sorbitol	24.50	4.900
NaOH	0.60	0.12
Water	472.8075	94.5615
Total	500.0000	100%
pH Specification	6.3-7.3	

Formulation A

	Months	Storage Conditions 21°C/45%	25°C/60%	30°C/70%
Content (%) of Dexamethasone	0	102.0		
	3	99.0	99.8	100.1
	6	99.6	101.6	101.1
	9	102.3	101.7	101.6
	12	99.7	98.3	97.6
	18	101.3	100.9	99.1
Decomposition (%) of Dexamethasone	0	0.2		
	3	0.2	0.2	0.2
	6	0.4	0.5	0.5
	9	0.5	0.5	0.6
	12	0.5	0.6	0.7
	18	0.7	0.7	0.8

Formulation B

	Months	Storage Conditions 21°C/45%	26°C/60%	31°C/70%
Content (%) of Dexamethasone	0	96.2		
	3	95.7	96.2	94.5
	7	95.8	94.7	92.5
	12	95.1	91.7	89.2
	18	86.3	86.0	83.9
Decomposition (%) of Dexamethasone	0			
	3	1.4	1.6	1.8
	7	2.4	2.9	3.1
	12	3.6	3.5	4.0
	18	10.7	11.2	12.9

These stability data convincingly show that if gel formulations of dexamethasone dihydrogenphosphate disodium are prepared at a pH value above 7.3, the formulations will provide a storage stability required for pharmaceutical preparations.

It is submitted it was unexpected that by adjusting the pH to alkaline values, as claimed, ophthalmic gel compositions of dexamethasone dihydrogenphosphate disodium could be obtained that (i) are storage stable and (ii) are not irritating to the human eye. Given that such gel formulations would prevent precipitation effects as encountered with ophthalmic solutions in general, such formulations are clearly not obvious and therefore inventive in view of Mazuel et al. alone or considered with Rozier.

A favorable action in the form of a Notice of Allowance is respectfully requested. The Examiner is invited to contact the undersigned to resolve any remaining issues.

Respectfully submitted,

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